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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,327	03/12/2007	Nariyoshi Shinomiya	VAN67 P-328A	7013

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EXAMINER	
WOLLENBERGER, LOUIS V	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,327	SHINOMIYA ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,8-20,38 and 48-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,8-20,38 and 48-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 10/7/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 4/7/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Applicant's amendment to the claims filed 10/7/2009 is acknowledged. With entry of the amendment, claims 2-4, 8-20, 38, and 48-50 are pending and examined herein.

An earlier communication acknowledged Applicant's election without traverse of Group I, claim(s) 1-20 and 38, drawn to an interfering RNA molecule having a sequence that is sufficiently complementary to a sequence of mRNA encoded by **human *c-met* (SEQ ID NO:1),** and to RNAi molecules, expression constructs, and vectors thereof, and to a method of use thereof for treating a *c-met* tumor or cancer in a subject. Also acknowledged was Applicant's further election of SEQ ID NO:15, "stable" expression vector, and si-hMet-Ad5^{221}.

With regard to claims 48 and 50, in the reply filed 2/13/2009 Applicant further elected "glioblastoma" tumor or cancer. The reply is fully responsive.

Claim Objections

Claims 19 and 20 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

The claims are drawn to a series of Ad5 vectors not reasonably embraced by the base claims, claims 4 and 10-18 as amended on 10/7/2009. As amended on 10/7/2009, claim 4 is limited to an interfering RNA comprising SEQ ID NO:15. The Ad5 constructs defined by claims 19 and 20 include vectors encoding several other siRNAs comprising sequences distinct from SEQ ID NO:15. See Table 2, at page 25 of the specification. The only construct in claims 19 and 20 reasonably drawn to the invention claimed in claims 4 and 10-18 is the Ad5(221) construct. Accordingly, the claims are drawn to products not embraced by any of the preceding claims from which they depend. Correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

MPEP 2173.05(s) states where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim.

In the instant case it has been noted the descriptors used to define the Ad5 constructs in claims 19 and 20 are not terms of art, but are Applicant's own designations of particular adenoviral constructs encoding different siRNAs. See Table 2, page 25 of the specification. The particular features of the adenoviral constructs recited in the claims could only be understood by

reference to a table and/or figure in the specification. However, there is no clear reason why the constructs could not be defined by words. Indeed, it is unclear how the limitation "si-hmet-AD5^{221}" adds any content to what has already been defined by the sum total of the claims 4 and 10-18 from which they depend, except, perhaps that the previous claims embrace any length of interfering RNA and almost any promoter whereas si-hmet-AD5^{221} specifically includes the U6 promoter and is designed to express a short interfering RNA of 19 bp in length comprising SEQ ID NO:15. Nevertheless, there is no practical reason why such features could not be recited in the claims. Base claim 4 defines the RNA sequence and additional claims already require an Ad5 viral vector construct comprising the DNA encoding said RNA sequence.

Accordingly, correction is required.

Claim Rejections - 35 USC § 102—withdrawn

The rejection of Claims 1-12, 14-17, and 38 under 35 U.S.C. 102(e) as being anticipated by Martinez et al. (US 20040265230 A1) is withdrawn in view of the Declaration under 37 CFR §1.131, filed 10/7/2009. The Declaration under 37 CFR 1.131, showing conception and reduction to practice of what is now claimed prior to Jan. 6, 2003, is sufficient to overcome the Martinez et al. reference.

Claim Rejections - 35 USC § 103—withdrawn

The rejection of Claims 19, 20, 49, and 50 under 35 U.S.C. 103(a) as being unpatentable over Martinez et al. (US 2004/0265230 A1), Shi et al. (US 2003/0180756 A1) and Abounader et al. (2002) *FASEB J.* 16(1):108-110 is withdrawn in view of the Declaration under 37 CFR 1.131 filed 10/7/2009.

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The rejection of Claims 1-20, 38, and 48-50 under 35 U.S.C. 103(a) as being obvious over Vande Woude et al. (US 2007/0020234 A1) in view of:

1. Martinez et al. (US 20040265230 A1).
2. Mroczkowski et al. (EP 1 243 596 A2) in view of:
3. Abounader et al. (2002) *FASEB J.* 16(1):108-110;
4. Tuschl et al. (US 2004/0259247 A1);
5. Elbashir et al. et al. (2002) *Methods* 26:199-213;
6. Shi et al. (US 2003/0180756 A1); and
7. Kaemmerer (US 2004/0162255 A1)

is withdrawn in view of the declaration under 37 CFR 1.131 filed 10/7/2009.

Double Patenting—withdrawn

The provisional rejection of Claims 1-20, 38, and 48-50 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over at least claims 9, 10, 22, 30, and 32 of copending Application No. 10/563,616 in view of:

1. Martinez et al. (US 20040265230 A1).
2. Mroczkowski et al. (EP 1 243 596 A2) in view of:
3. Abounader et al. (2002) *FASEB J.* 16(1):108-110;
4. Tuschl et al. (US 2004/0259247 A1);
5. Elbashir et al. et al. (2002) *Methods* 26:199-213;
6. Shi et al. (US 2003/0180756 A1); and

7. Kaemmerer (US 2004/0162255 A1)

is withdrawn in view of the amendments to the claims filed 10/7/2009.

Claim Rejections - 35 USC § 103—new

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4 and 8-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godowski et al. (US Patent 5,316,921) in view of:

1. Livache et al. (US Patent 5,795,715);

2. Gregory et al. (US Patent 5,932,210);

3. Barber et al. (US Patent 5,716,832); and
4. Good et al. (1997) "Expression of small, therapeutic RNAs in human cell nuclei" *Gene Therapy* 4:45-54.

The instant claims use open "comprises" language to define the interfering RNA of claim 4, impose no length restrictions on the interfering RNA comprising SEQ ID NO:15, and embrace DNA expression cassettes and recombinant constructs encoding dsRNAs comprising SEQ ID NO:15.

As shown by the alignment below, Godowski et al. had disclosed a 56-nucleotide DNA probe that comprises the complete antisense complement of instant SEQ ID NO:15 (Qy). The probe is disclosed for the detection of mRNA and/or cDNA sequences encoding human hepatocyte growth factor receptor and portions thereof (column 21, lines 45-60).

Godowski et al. does not teach or suggest dsRNAs comprising SEQ ID NO:15 or sequences comprising SEQ ID NO:15. However, one of skill would reasonably have been led to make and use dsRNAs comprising SEQ ID NO:15 in view of the prior art.

For example, Livache et al. had taught a process for making and using short (40 to 100 base-pair) double-stranded RNA fragments for diagnosis, and in particular for the detection of target nucleic acid sequences in a biological sample (see entire disclosure, including col. 3, lines 44-50; col. 4, lines 54-65; col. 5, beginning at line 54 and bridging to col. 6). See claims also. It is said he dsRNAs may may include one or more single stranded ends (col. 7, lines 15-21, 30-32). Methods for preparing DNA constructs comprising suitable RNA polymerase promoters and encoding dsRNAs of betweeen 40 and 100 base pairs are also disclosed (see Detailed Description of Preferred Embodiments, beginning at col. 2).

Accordingly, in view of Livache et al., it would have been prima facie obvious to make and use the cDNA probe (SEQ ID NO:17) disclosed by Godowski et al. in the form of a dsRNAs and DNA cassettes encoding said dsRNAs for the detection and/or quantification of human hepatocyte growth factor gene sequences according to the method and for the reasons disclosed by Livache et al. for any of the purposes relating to the research and use of of human hepatocyte growth factor sequences discloed by Godowski et al. Such dsRNAs and double stranded DNA constructs comprising the SEQ ID NO:17 probe of Godowski et al. would necessarily also comprise the 56-nucleotide RNA or DNA sequence complementary to SEQ ID NO:17, which sequence would necessarily comprise instant SEQ ID NO:15. As the dsRNAs comprising SEQ ID NO:15 meet each of the structural requirements of the instant claims, they necessarily comprise all physical and chemical properties inherent to such structures, and are reasonably considered to be interfering RNAs, as evidenced by the claims (3 and 4, for example). Therefore, the prior art had reasonably suggested interfering double stranded RNA molecules within the scope of what is now claimed.

```
RESULT 1
US-07-884-811-17/c
; Sequence 17, Application US/07884811
; Patent No. 5316921
;  GENERAL INFORMATION:
;    APPLICANT:  Godowski, Paul J.  Lokker, Nathalie A.  Mark, Melanie R.
;    TITLE OF INVENTION:  SINGLE-CHAIN HEPATOCYTE GROWTH FACTOR VARIANTS
;  INFORMATION FOR SEQ ID NO:  17:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  56 bases
;      TYPE:  NUCLEIC ACID
;      STRANDEDNESS:  single
;      TOPOLOGY:  linear
US-07-884-811-17

  Query Match            100.0%;  Score 19;  DB 2;  Length 56;
  Best Local Similarity   100.0%;  Pred. No. 5.4;
  Matches   19;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GTGCAGTATCCTCTGACAG 19
              |||||||||||||||||||
Db         43 GTGCAGTATCCTCTGACAG 25
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SEQ ID NO:15 shown below for reference.

<210> 15
<211> 19
<212> DNA
<213> Homo sapiens

<400> 15
gtgcagtatc ctctgacag

While Godowski et al. and Livache et al. as a whole do not teach or suggest Pol III promoters in general or U6 promoters in particular, or adenoviral Ad5 vectors for synthesis of cDNA probes or dsRNAs, these elements were known and conventional in the prior art of recombinant DNA technology. It would therefore have been obvious to use any of these known options to prepare DNA constructs of the type generally described by Livache et al. for synthesizing and preparing dsRNA fragments for the uses disclosed by Livache et al.

For example, Gregory et al. had disclosed methods for making and using recombinant adenoviral Ad5 vectors.

Barber et al. had disclosed methods for making and using recombinant retroviral vectors.

Finally, Pol III and U6 promoters specifically had been disclosed in the prior art as particularly useful for the synthesis of short RNAs, including small ribozymes, antisense oligoribonucleotides, and RNA aptamers, as shown by Good et al. One of skill in the art would reasonably have inferred that U6 promoters could similarly be used to drive the synthesis of complementary RNA sequences of 40 to 100 nucleotides in length in the manner suggested by Livache et al., who had suggested using DNA constructs with any suitable promoter for the synthesis of dsRNAs (col. 1, lines 55-60).

Thus, as a whole, the prior art had suggested making and using dsRNAs comprising SEQ ID NO:15 within the scope of what is now claimed.

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Claims 2-4, 8-20, 38, and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abounader et al. (2002) *FASEB J.* 16(1):108-110; Mroczkowski et al. (EP 1 243 596 A2); Elbashir et al. et al. (2002) *Methods* 26:199-213; and Tuschl et al. (US 2004/0259247 A1); the combination in view of Shi et al. (US 2003/0180756 A1).

Upon further consideration, in view of the general principles and specific rules disclosed in the prior art (Tuschl et al. and Elbashir et al.) at the time of invention, describing step-by-step procedures for selecting, making, and using short interfering RNAs (siRNAs) for inhibiting the expression of any known gene, and given that the siRNA comprising SEQ ID NO:15 would have been one of a number of a finite set of siRNAs that would have been identified during the ordinary course of applying these design rules to select candidate siRNAs for inhibiting the expression of the human c-met gene (NM_000245), the sequence of which was known in the prior art, there is sufficient evidence to believe one of skill would necessarily have been led to a list of candidate siRNAs for inhibiting human c-met that included the siRNA comprising SEQ ID NO:15.

Claim interpretation:

The claims embrace double stranded, interfering RNA molecules of 19 to 29 base pairs in length, having 2-nt, 3' overhangs, comprising the 19-nt sense sequence (5'-gtgcagtatcctctgacag-

3'), referred to in the claims as SEQ ID NO:15, which is contained in GenBank Acc. No. NM_000245 at positions 3257 to 3277 (see relevant portion below). The term "siRNA" is described at page 19 of the specification.

The claims require no extraordinary activity or level of RNAi. In fact the only functional language in the claim is found in the term "siRNA." The method claims 38 and 48-50 require inhibiting the expression of c-met and thereby inhibiting tumor cell growth. An interfering RNA, as understood in the art at the time of invention, would reasonably embrace any short RNA duplex that produces a measurable decrease in the mRNA and/or protein level, whether the decrease is suitable for phenotypic or therapeutic studies or not. The Examiner finds no special meaning in the specification to teach an "siRNA" should be understood to mean otherwise. Thus, the prima facie showing below does not and need not show one of skill would expect to observe greater than 50% inhibition based on the selection criteria known at the time, but that, on its face, one of skill would reasonably expect the RNA duplex selected would induce RNAi.

The rejection:

The mRNA sequence encoding human met proto-oncogene (hepatocyte growth factor receptor) was known in the prior art, as shown by Mroczkowski et al. and Abounader et al., describing the mRNA sequence corresponding to instant SEQ ID NO:1 encoding human c-met (hepatocyte growth factor receptor). See page 8 of Mroczkowski et al., showing the full length sequence of c-met and identifying the sequence as that of GenBank Acc. No. NM_000245; and see the report by Abounader et al., describing ribozyme sequences targeted to human c-met. Also well known were the relevant identifying characteristics of the human c-met mRNA, such as the

locations of the start and stop codons, 5' and 3' UTRs. For example, GenBank Accession No. NM_000245 denotes the start codon at position 189.

As further shown by Mroczkowski et al. and Abounader et al., the correlation between c-met expression and several different human carcinomas, including glioblastomas, was well established. Each had taught that inhibiting c-met expression inhibits and sometimes reverses cancer cell growth. See pages 2 and 3 in Mroczkowski et al., and entire disclosure of Abounader et al. More specifically, Abounader et al. showed the growth human glioblastoma cells in culture and in animals may be effectively inhibited using adenoviral expression constructs encoding ribozymes targeted to the human c-met gene. It is said, for example, treatment of animals bearing intracranial glioma xenografts with anti-SF/HGF and anti-c-met U1snRNA/ribozymes by either intratumoral injections of adenoviruses expressing the transgenes or intravenous injections of U1snRNA/ribozyme-liposome complexes substantially inhibited tumor growth and promoted animal survival.

Accordingly, one of skill would have had ample reason to make and use inhibitors of c-met expression, including any nucleic acid-based inhibitor, to further investigate the role of c-met in human cancers, identify drugs capable of inhibiting c-met function, and to effectively treat cancer in humans suffering from c-met dependent cancer. To this end, one of skill would have been motivated to make and use the most effective nucleic acid based inhibitors known and available at the time. These included short interfering RNAs, or siRNAs, which were well known in the prior art for their ease of use, potency, and utility for suppressing gene expression in cells in vitro and in vivo for both research and therapeutic purposes.

At the time of invention, RNA interference was a well established tool for investigating gene function in cells in culture, and methods for designing and using short interfering RNAs for inhibiting the expression of any gene were well known in the art, as evidenced by Tuschl et al. and Elbashir et al.

Each reference teaches that, fundamentally, target-specificity depends on Watson-Crick base pairing to the target. Thus, the complete genus of all possible siRNAs is described by the sequence of the mRNA target. The genus is further narrowed by selecting those siRNAs that meet the criteria set forth by, for example, Elbashir et al., who taught a step-by-step procedure for selecting candidate siRNAs from a known mRNA sequence, wherein the siRNAs are selected from the ORF preferably 50 to 100 nt downstream of the start codon, avoiding the 5' and 3' UTRs and sequences close to the UTRs (page 202). The practitioner searches for sequences of the type AA(N19)UU, choosing those that have G/C contents of approximately 50%, or at least between 32 and 79%. The siRNAs preferably comprise 21-nt sense and antisense strands with 2-nt 3' overhangs. The authors state they prefer to select target regions such that siRNAs sequences may contain uridine residues in the 2-nt overhang (page 201). The final collection of candidate siRNAs is then BLASTed to select those having sequence specificity with the target (page 201, 202, and Fig. 2). At page 201, Elbashir et al. et al. taught that, while selection of the targeted region is currently a trial-and-error process, there is a likelihood of 80-90% success given a large enough random selection of target genes. Accordingly, the prior art suggested that siRNAs designed in silico according to these basic rules could reasonably be expected to trigger sequence-specific RNAi in cells in culture.

Tuschl et al. had taught that siRNAs may be from 19-25 nucleotides in length and are useful for both research and therapeutic purposes. It is said siRNAs have advantages over conventional antisense oligonucleotides and ribozymes. For example, at paragraph 148 it is said siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments. Thus, it was further known in the art at the time that RNA duplexes of 19-23 base pairs in length were, on the whole, suitable for RNAi studies in mammalian cells, each being capable of causing significant reduction in mRNA target expression (see Figs. 12 and 13 and see discussion at paragraphs 162-4 in Tuschl et al.). Furthermore, duplexes as long as 24- and 25-base pairs are also said to be efficient for RNAi in mammalian cells, the relative activity depending on the length of the 3' overhangs (paragraph 7; Fig. 12; and paragraph 162).

Thus, the scope and contents of the prior art suggests that one of skill would have readily envisioned the set of candidate siRNAs satisfying these criteria for the human c-met sequence disclosed by Mroczkowski et al., and GenBank NM_000245 (MPEP 2144.08).

As evidenced by the relevant portion of GenBank NM_000245, reproduced below, the instantly claimed interfering RNAs comprising SEQ ID NO:15 are complementary to positions 3257 to 3277 of GenBank NM_000245. As evidenced by the sequence, the 19-nucleotide SEQ ID NO:15 sequence is at least 100 nucleotides downstream of the start codon and is directly downstream of an AA dinucleotide (underlined), as recommended by Elbashir et al., and has a GC content within the range recommended by Elbashir et al.

NM_000245:

3241 cggttcatgc cgacaagtgc agtatcctct gacagacatg tcccccatcc taactagtgg

SEQ ID NO:15 gtgcagtatcctctgacag

Accordingly, in view of the totality of the evidence, one of skill scanning the c-met mRNA sequence of NM_000245 for candidate siRNAs would have envisoned the set of 19-25 nt siRNAs targeting the AA(N19) target site region defined by the AA at position 3255. The siRNAs against this region would necessarily have been identified by application of the Elbashir et al. rules, which had defined the standard for selecting siRNAs at the time of invention, and would necessarily have comprised a sense strand that comprised instant SEQ ID NO:15 and a GC content of approximately 50%.

Thus, siRNAs within the scope of the instant claims, targeting instant SEQ ID NO:15, satisfy the criteria of Elbashir et al. and Harborth et al., and would therefore have reasonably been expected to interfere with the expression of human c-met in a mammalian cell in culture, as taught by Tuschl et al., Elbashir et al., and Harborth et al. One of skill would therefore have had reason to make and use these siRNA(s), as well as any other siRNA in the genus satisfying these criteria, to inhibit the expression of human c-met in vitro and in vivo for research and therapeutic purposes to investigate the function of the gene and to inhibit the expression of cancer cells, as taught by Elbashir et al., Harborth et al., and Tuschl et al.

MPEP 2144.09 states that a *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). The

Examiner submits the facts of the instant case are analogous, inasmuch as one of skill at the time interested in investigating human c-met function and inhibiting cancer cell growth would have been motivated to select and use siRNAs using the criteria set forth at the time by Harborth et al. and Elbashir et al. While the genus of all possible siRNAs selected according to these criteria may well have been large, the genus was, nevertheless finite, defined and limited by the human c-met coding sequence (NM_000245); *a priori* each siRNA would have been considered equivalent, one to the other, inasmuch as each could be used for the same purpose, leading one of skill to make and use any one of these siRNAs with the expectation each would be capable of performing the function intended (MPEP 2144.06.II). The Examiner knows of no disclosure in the prior art clearly suggesting that the majority of siRNAs selected according to the Elbashir et al. criteria fail to produce RNAi. Rather, there is the reasonable expectation that many if not the majority would elicit RNAi at some level. Obviousness does not require absolute predictability, and predictability is determined at the time the invention was made (MPEP 2143.02).

In the instant case, the prior art suggested that short double stranded RNAs satisfying the structural criteria of Elbashir et al. and Harborth et al. would interfere with mRNA expression. Therefore, there is sufficient evidence to suggest one of skill would have had reason to make a 19-23-nt siRNA within the scope of the claims to investigate the function of human c-met in culture with the expectation the siRNA would have the property and utility associated with such compounds: namely, RNA interference activity.

Accordingly, the instantly claimed siRNAs are considered prima facie obvious in view of the scope and contents of the prior art suggesting these siRNAs.

The Examiner notes this *prima facie* case of obviousness based on structural similarity is rebuttable by proof that the claimed siRNA(s) possess unexpectedly advantageous or superior properties (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)). The proof must be commensurate in scope with what is claimed.

Moreover, as shown by Abounader et al. and, in more detail, by Shi et al., methods and materials for making and using recombinant adenoviral (transient) and retroviral (stable) vectors, comprising Pol III promoters such as the U6 promoter, for the expression of short therapeutic nucleic acids such as ribozymes and short interfering RNAs in mammalian cells was also well established in the prior art as an effective means for suppressing the expression of virtually any known gene for research and therapeutic purposes. Abounader et al. specifically demonstrate the use of adenoviral constructs encoding ribozymes targeted to c-met for inhibiting the growth of glioblastoma cells in vitro and in vivo. Shi et al. provide a complete blueprint for preparing and using Pol III-driven adenoviral and retroviral expression vectors encoding short interfering RNAs (see entire disclosure). The Ad5 replication-incompetent genome is expressly recommended (see paragraph 125 in Shi et al. and Materials and Methods in Abounader et al., citing the Ad5-based method of Vogelstein et al.).

As shown by Abounader et al., methods for delivering siRNA-encoding adenoviral vectors and other vectors into the brains of patients for the knockdown of specific disease-associated genes were also well established and enabled by the prior art (see Materials and Methods and Results sections in Abounader et al.).

Accordingly, the prior art clearly suggested the instantly claimed siRNAs for inhibiting c-met expression for both research and therapeutic purposes to treat cancer. In view of the

disclosure by Abounader et al. showing that the inhibition of c-met expression in human glioblastoma cells effectively inhibits the growth of said cells in culture and in living animals, and in view of the known potency of short interfering RNAs for accomplishing the same function, one of skill would have reasonably predicted that direct infusion of siRNAs or adenoviral vectors encoding said siRNAs into the brains of patients with glioblastoma cells would, similarly, result in the inhibition of glioblastoma cells in said patients thereby providing for a treatment of a human cancer. Moreover, in view Mroczkowski et al., one of skill would have further been motivated to make and use c-met siRNAs and vectors thereof to further investigate the role of c-met in several other types of human cancers in cells in vitro and in vivo, and perhaps develop strategies to treat such cancers and improve the human condition, obtaining all the known advantages of adenoviral and retroviral expression, including stable and long term expression.

Thus, the prior art as a whole had reasonably suggested short double stranded interfering RNAs comprising SEQ ID NO:15 for inhibiting the expression of human c-met for both research and therapeutic purposes as in the inhibition glioblastoma cells in vivo.

Response to Applicants' Arguments

Applicants' arguments presented on 10/7/2009 not specifically addressed above are considered to be moot in view of the new rejections stated herein, above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore can be reached on (571)272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Louis Wollenberger/
Primary Examiner, Art Unit 1635
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